90. Cystic lung diseases: lung granulomatosis

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Pulmonary Langerhans' cell histiocytosis (PLCH): A new UK register

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Introduction: PLCH is a rare interstitial lung disease, linked to cigarette smoking and may be associated with respiratory failure and death. Limited UK data has been published and little knowledge exists of the diagnostic and treatment practices employed by UK physicians.
Aims and objectives: Our study aims to characterise the epidemiological, clinical, histological, radiological and prognostic indicators in a UK cohort of patients with PLCH.
Methods: 112 cases from 53 centres (65 from the BTS British Orphan Lung Disease database and 47 new or previously unregistered). Consultants provided contact details; Patients were sent an information leaflet, consent form and questionnaire. Once consent obtained, consultants were sent a medical questionnaire. The patients' GP provided current medication and medical history.
Results: Details on 95 patients (19 deceased, 7 lost to follow-up) received. Clinical information regarding 67 cases has been received; completed by the patient, consultant or both (31 males). Age at presentation 37.1 years (SD 14.4). *Presenting symptoms:* Dyspnoea 78%, cough 63%, constitutional symptoms 25%, pain 22% and pneumothorax 8%, *Smoking status:* Ex 71.7%, current 25.0% mean (SD) 19.9 (16.9) pack years. Cannabis use 9.6% *Diagnosis:* 93.8% patients had had an HRCT scan and 61% an open lung biopsy. *Disease course:* Symptoms resolved 23.3%, same 33.3% and 43.3% had slowly progressed. *Treatment:* None 56%, Steroids 29.6% immunosuppression/chemotherapy 26.5%. pleural surgery 18.7% and lung transplant 6%
Conclusions: This UK dataset indicates a high prevalence of smoking in our cohort and, despite advances in computed tomography a high percentage of patients are still diagnosed with an open lung biopsy.

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Pulmonary findings of the patients with Sjogren syndrome

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Background: Sjogren syndrome is a chronic and autoimmune disease characterized by lymphocytic infiltrates in all exocrine glands. Dryness of the eyes and mouth are the most common symptoms of this syndrome. Primary pulmonary manifestations of Sjogren syndrome are diffuse lung and airway diseases.
Aim: 131 patients were included in our study between the years 2000-2011 who were diagnosed with Sjogren syndome. Of these patients, 31 were examined who admitted to pulmonary diseases clinic and had Thorax computed tomography (CT). We aimed to evaluate demographic characteristics, respiratory symptoms, pulmonary function test parameters and Thorax CT findings of patients who have Sjogren Syndrome.
Results: The mean age was 57.3 years and 30 (%96.8) were women. Pulmonary function test was normal in %45.2 of the patients. 7 patients (%22.6) were smoker. 2 patients had COPD and 4 had asthma. 11 patients suffered from dyspnea and 5 from coughing. Thorax CT revealed pathological findings in 22 patients (%71.0). In Thorax CT examination 8 atelectasis, 8 pulmonary nodules, 5 pathological lymph nodules, 3 bullae formation, 2 bronchiectasis, 2 pulmonary embolism, 2 fibrosis, 2 infiltration, 2 ground glass appearence and 2 pleural effusion were reported. Of the 23 patients who underwent echocardiographic evaluation 7 (%22.6) had elevated systolic pulmonary artery pressure (mean 63.3 +27.8mmHg).
Conclusion: Respiratory disorders are common in patients with Sjogren syndrome even if the affected individuals are asymptomatic. Therefore, close follow up of these patients in pulmonary disease clinics are recommended and Thorax CT assessment for lung involvement should be considered for early diagnosis.

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Characterization of 76 patients with lymphangioleiomyomatosis from a Brazilian reference center

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Introduction: Lymphangioleiomyomatosis (LAM) is a rare disorder affecting childbearing women. There was no previous epidemiological study from South America characterizing subjects with LAM.
Objectives: To describe the clinical features, quality of life (SF-36 questionnaire), pulmonary function tests (PFT) and VEGFD data, and also six-minute walk test (6MWT) performance of LAM patients followed in a Brazilian reference center.
Methods: Data from 76 women with LAM followed in the Pulmonary Division of the University of Sao Paulo from 2008 to 2011 were reviewed.
Results: The mean age was 42±11 years. The average age at diagnosis was 38±9 years, whereas the mean time from first symptom to diagnosis was 23 months. The diagnosis of LAM was confirmed by tissue biopsy in 88% of cases. 14% of patients had tuberous sclerosis, 50% renal angiomyolipoma, 61% previous pneumothorax and 15% previous chylothorax. Dyspnea was a complaint of 69% of subjects and 20% were ex-smokers. Impaired quality of life was found, with worse scores in physical and emotional domains. Mean FEV_1 and D_LCO were, respectively, 74±26%pred and 65±28%pred. The most common abnormalities on PFT were obstructive pattern (58%), reduced D_LCO (53%) and air trapping (22%). The mean distance walked was 493±118 m, while the mean Borg dyspnea score and the minimum SpO_2 at end 6MWT were, respectively, 3±3 and 88±9%. Dessaturation ≥4% was found in 53% of patients during 6MWT. In 60% of subjects, VEGFD serum level was increased.
Conclusions: In a Brazilian sample of LAM patients, besides the typical results in PFT, quality of life impairment, increased VEGFD serum levels and dessaturation during 6MWT were also important findings.

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Rate of FEV1 decline in lymphangioleiomyomatosis associated with tuberous sclerosis complex

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Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease characterized by proliferation of abnormal TSC1/2-mutated smooth muscle cells in the lung parenchyma, leading to progressive cystic destruction, lung function decline, and respiratory insufficiency. LAM may be either sporadic (S-LAM) or associated with the tuberous sclerosis complex (TSC-LAM). Cross-sectional studies have suggested that TSC-LAM is less severe than S-LAM, but no longitudinal data are available. We retrospectively compared the rate of FEV1 decline in 16 patients with TSC-LAM and 53 patients with S-LAM diagnosed according to ERS 2010 criteria with a lung function follow-up ≥1 year. Results are shown below.

	TSC-LAM (mean±SD)	S-LAM (mean±SD)	p value
n	16	53	
Women, %	94	100	
Age at LAM diagnosis, yr	33±11	40±10	0.004
Initial FEV1, %pred	72±25	70±26	NS
Lung function follow-up, yr	5.9±5.2	5.3±3.8	NS
FEV1 decline %pred/yr	–2.8±2.8	–3.4±5.0	NS
FEV1 decline ml/an	–103±89	–114±177	NS

Conclusion: Although diagnosed at an earlier age than S-LAM, patients with TSC-LAM had similar mean FEV1 at diagnosis, and similar mean rate of FEV1 decline. Lung function follow-up similar to S-LAM may be recommended in TSC-LAM.

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Effect of source of inhalation antigen on manifestation and prognosis of EAA patients

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Exposure to moulds in domestic environment leading to EAA is often reported. Inhalation exposure to moulds may lead to developement of profibrotic Th2 cells.
Aim of the study: To examine influence of inhalation antigen on EAA manifestation and prognosis.
Method: Fifty-four patients of the mean age 55,9±17,5 were included to the retrospective study. They underwent complex diagnostic program including detailed history assessement, physical examination, serum specific IgG tests, lung functions tests (spirometry, diffusing capacity of the lung for CO), HRCT of the chest, bronchoscopy with BAL and TBB. Patients were divided into five groups according to their antigen exposure history – unknown source of exposure, professional exposure in chemical industry workers, exposure to moulds, exposure to bird antigens and exposure to mammal's fur and epithelium.
Results: Patients with mould exposure history had significantly higher FVC ($p<0,05$), FEV1 ($p<0,01$) and Dlco ($p<0,01$) at the time of diagnosis than other groups. Significant improvement of FVC and Dlco was detected in the patients with history of exposure to bird antigens. We found no difference in BALF differential cell counts among patient groups. BALF PMN cell count at the time of diagnosis negatively correlated with FVC and FEV1 a year after diagnosis in the whole group ($p<0,05$).
Conclusion: EAA caused by moulds does not have a worse manifestation and prognosis that EAA caused by other inhalation antigens. Better outcome of patients exposed to bird antigens is probably influenced by easy removal of the antigen's source. The type of inhalation antigen very likely does not influence the manifestation of EAA.

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Diagnostic yield of specific inhalation challenge in patients with hypersensitivity pneumonitis

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Introduction: Hypersensitivity pneumonitis (HP) is a potentially serious illness that may progress to pulmonary fibrosis and chronic respiratory insufficiency. Reliable methods are needed to diagnose the condition and, if possible, to identify the causative agent. The aim of the study was to stablish the diagnostic yield of Specific Inhalation Challenge (SIC) in patients with HP.
Material and methods: All patients with suspected HP in whom SIC were performed between June 1995 and December 2010 (n= 113) were included. Diagnosis of HP was established on the basis of internationally accepted criteria (*M.Girard, et al. Allergy 2009; 64:322-334*). The SIC was considered positive in the case of a decrease >15% in FVC and/or a decrease >20% in TLCO, or a decrease in FVC between 10-15% accompanied by an increase in temperature of 0.5°C within 24h of the inhalation of the antigen (*Morell F, et al. Medicine 2008; 2:110-130*).
Results: Eighty-eight patients were diagnosed with HP. In 68 the SIC was positive and in 45 negative; four false positives (3.5%) and 24 false negatives (21.2%) were recorded. The sensitivity and specificity of the test were 72.7% and 84% respectively, with a positive predictive value of 94% and a negative predictive value of 47%. Having HP caused by an antigen other than birds or fungi was a predictor of a false negative result (p=0.035).
Conclusions: In HP a positive SIC practically confirms the diagnosis, while a negative result does not rule it out.
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Computer tomography lung density in smokers is correlated to measures of local inflammation in the lung

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Cigarette smoking causes an inflammatory response in the lungs. CT imaging provides means of quantifying pulmonary structure and function. We hypothesized that the inflammation in smokers may be mirrored both by an altered attenuation on CT and by measures inflammation in the lungs.
Materials: Healty smokers (20 men, 20 women, mean age 54, 35±12 pack years, 40 healthy neversmokers, age 57 and 40 COPD, age 59 (38±11 PY, 31 current smokers, 9 exsmokers) performed inspiratory CT scans. Values between -500 and-750 HU were considered as high attenuation area. BAL, was performed. Cell concentration were mesured.
Result: Attenuation for smokers (44% ± 5.7) and neversmokers (38% ± 5.6), COPD exsmokers (33% ± 4.5) ($p<0.001$ and $p<0.05$ respectively). COPD smokers (41% ± 5.0) did not differ from that of healthy smokers. Both smoker groups (healthy smokers: 556±259 x 10^6/L (mean±SD); COPD smokers: 458±263) had higher cell concentration in BAL compared to neversmokers (121±50) and COPD exsmokers (100±29). The difference between the smoking and nonsmoking groups were significant ($p<0.001$). There was a significant correlation ($p<0.0001$) between cell concentration in BAL and CT attenuation, There was no significant correlation between cell concentrations in BAL and CT attenuation in neversmokers and COPD exsmokers.

Conclusion: The increased lung density in smokers compared to nonsmokers may mirror an inflammatory response induced by cigarette smoke. This hypothesis is strengthened by a positive correlation between lung attenuation and cell concentration in the lower respiratory tract. Our results provide a quantitative approach for measuring smoke-related structural changes in the lung.

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Different cutoff values of serum SP-D for German and Japanese to diagnose idiopathic interstitial pneumonias are related to different SFTPD gene polymorphisms

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Introduction: Surfactant protein (SP) -D is a member of the C-type lectin superfamily. Serum SP-D is applied as a diagnostic biomarker for various interstitial lung diseases in Japan, but not in European countries. It is also known that rs721917 single nucleotide polymorphism (SNP) in surfactant protein D (SFTPD) gene might influence serum SP-D levels.
Aims: This study was aimed to evaluate serum levels and genetic backgrounds of SP-D both in German and Japanese cohorts.
Methods: Serum levels of SP-D were measured and compared between patients with idiopathic interstitial pneumonias (IIPs) and healthy subjects (HS) both in German and Japanese cohorts. In addition, rs721917 SNP was genotyped by polymerase chain reaction. The power of serum SP-D to discriminate IIPs from HS was examined by receiver operating characteristic analysis based on ethnicity and rs721917 genotype.
Results: The serum levels of SP-D in IIPs were significantly higher than in HS for both German and Japanese cohort (both $p<0.001$). The discriminating cutoff values of serum SP-D were higher in the German than in the Japanese cohort. Furthermore, the T/T genotype of rs721917 SNP, which is more frequent in German HS than in Japanese HS, was correlated with high levels of serum SP-D, and the cutoff value of serum SP-D was different according to rs721917 genotype.
Conclusions: Our data suggest the possibility of serum SP-D to be used as diagnostic biomarkers for IIPs in Germans. The cutoff value of serum SP-D is higher in the German than in the Japanese cohort, and this difference might be related to the difference of rs721917 genotype distribution.

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Sarcoidosis associated pulmonary hypertension (SAPH) in the Netherlands

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Background: The development of pulmonary hypertension (PH) is an important risk factor for early mortality in sarcoidosis. The prevalence is of SAPH in Europe is largely unknown.
Aim: To investigate the prevalence of and clinical parameters associated with SAPH in the Netherlands.
Methods: We analyzed clinical data and transthoracic echocardiograms (TTEs), made routinely at our PH/Interstitial Lung Disease clinic, from consecutive patients. Sarcoidosis patients with reliable echocardiography, without left heart dysfunction, were included. An estimated systolic pulmonary artery pressure (sPAP) > 50 mmHg was considered PH. Possible PH was defined as sPAP 37-50 mmHg or sPAP ≤ 36 mmHg with signs of right ventricular dysfunction.
Results: From 139 sarcoidosis patients, 130 were included with stage 0 (11), I (46), II (39), III (7), IV (16). 5 patients (3,8%) had PH and 6 (4,6%) possible PH. Patients with PH were all women, predominantly black (4 out of 5) with stage IV disease (4 out of 5). 4 out of 6 patients with possible PH (3 white, 3 Asian) had stage I disease.
TLCO % pred was lower in PH compared to no PH (median: 46,0 (18- 47) vs 78,50 (29,0- 119) $p < 0,01$). FEV1% pred was decreased in PH compared to no PH (median: 48,0 (36,0- 96,0) vs 82,0 (30,0- 131,0) $p< 0,05$). TLC was decreased in PH (median: 61,0 (51,0- 91,0) vs 82,50 (46,0- 116)), but not significantly different. In possible PH pulmonary function showed no significant difference versus no PH.
Conclusions: SAPH is uncommon in the Netherlands and mainly found in black women with stage IV disease and associated with decreased lung function. Unexpectedly, suspicion of PH was found in some patients with stage I disease, warranting further investigation.

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The influence of TNFα gene polymorphism on the therapeutic response in patients with sarcoidosis

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Sarcoidosis is an inflammatory disease of unclear etiology, with genetic factors playing a considerable factor in both its onset and clinical presentation. In the majority of patients, the disease goes away spontaneously, without treatment. However, longer therapy is necessary in a small number of patients.
The aim of this research was to determine the role of TNF-α-308G/A polymorphism in the therapeutic response in patients with sarcoidosis. The research encompassed 66 patients with sarcoidosis, 44 of whom were females and 22 were males, of average age 51,17±11,22, who were treated for sarcoidosis at the Clinic for Lung Diseases Niš. TNFα-308 G/A gene polymorphism was examined in all patients using the PCR-RFLP method.
Results: 10 patients received no treatment, 48 patients underwent corticosteroid treatment, while 8 patients received combined treatment using corticosteroids and methotrexate. No statistically significant difference in the distribution of TNF-α gene polymorphism genotypes and alleles was detected between the patients receiving corticosteroid treatment and those without treatment. However, the duration of the treatment was statistically considerably lower in patients belonging to AA genotype group (14.83±9.77) when compared to those from GG genotype group (18.03±10.56), $p<0.05$.
Conclusion: Previous research showed that the presence of TNF-308A allele is a good prognostic sign of sarcoidosis, as it is coupled with the acute form of the disease and the absence of recidives. Our results indicate a great pronostic significance of this allele, given that its presence could predict a favorable outcome of the disease and a shorter duration of treatment.

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Determinants of fitness to fly in interstitial lung disease

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Introduction: The predictors of in-flight hypoxia in interstitial lung disease remain unknown. The hypoxic challenge test (HCT) is widely used to evaluate fitness to fly. We assessed the determinants of a positive HCT in patients with ILD.
Methods: 183 patients underwent HCT in 2005-2011 (74 males; mean age 57.6; 73 ex-smokers) of which 126 had idiopathic interstitial pneumonia, 26 hypersensitivity pneumonitis, 23 sarcoid and 8 other ILDs. 164 had lung function tests on the same day, 124 had an echocardiogram within 1 year. The HCT was performed using an inhaled gas mixture containing 15% oxygen. From BTS guidelines, the HCT was positive (in-flight oxygen required) if PaO_2 < 6.6 kPa on 15% oxygen.
Results: Median PaO_2 on air was 10.3 kPa (range 8.2-14.3), with median percent predicted FVC 68.1% and DLCO 38.3%. On univariate logistic regression, variables associated with a positive HCT were age ($p=0.04$), PaO_2 on air ($p<0.0001$), FVC%, DLCO% and composite physiologic index (CPI) (p for all<0.00001). Pulmonary hypertension (PH) on echocardiogram was also predictive, although less strongly ($p=0.015$). On multivariate analysis, variables remaining significantly associated with a positive HCT were PaO_2 on air ($p<0.0001$), lung function markers including CPI ($p<0.0001$), or in separate models DLCO ($p<0.0001$), and FVC ($p=0.006$), while PH on echo was no longer predictive ($p=0.13$). On ROC analysis, area under the curve was 0.80 for PaO_2 on air, 0.75 for DLCO%, 0.72 for CPI, 0.83 for combined CPI and PaO_2, and 0.85 for combined DLCO and PaO_2.
Conclusion: Our findings highlight the potential of PaO_2 on air, DLCO and CPI levels as non-invasive predictors of fitness to fly. Identifying the best combination requires further prospective evaluation.

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Diagnostic yield of transthoracic lung biopsy guided by CT in diffuse lung disease

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Introduction: Diffuse Lung Diseases (DLD)encloses a large and heterogeneous group of diseases, which diagnosis is based on a multidisciplinary approach that sometimes requires histology. Transthoracic Lung biopsy (TTLB)guided by CT have been scantily used in this context and its actual diagnostic value is unknown.
Objective: Analysis of the diagnostic yield and complications of TTLB guided by CT and its relevance in the multidisciplinary diagnostic approach of DLD.
Methods: Retrospective review of 56 patients clinical files with DLD, who were submitted to TTLB guided by CT between January 2009 and November 2011. Trucut18-20Gauge needles, percutaneous anesthesia and multislice CT Siemens Somatom were used.
Results: The patients included had an average age of 58.4 years and 32 (57%) were male. Diffuse micronodular was the most frequent CT pattern observed in 41.1% patients, consolidation in 25%, ground glass in 14.3%, reticular in 14.3% and cysts in 5.3%. Biopsy confirmed preliminary diagnostic hypothesis in 27 (48.2%) patients and in 13 (23.2%) histological features observed guided to another diagnosis, leading to a diagnostic sensitivity of 71,4% (40/56 patients). In 16 (28.6%) patients this procedure was not conclusive. Diffuse micronodular and consolidation were the higher diagnostic yield patterns. 11 patients had complications, 7 pneumothorax and 4 non-massive hemoptysis. Organizing pneumonia (35%), sarcoidosis (12%) and silicosis (10%) were the most frequent diagnosis.
Conclusions: In this series of patients TTLB guided by CT was safe, quick and

with high diagnostic accuracy, suggesting that should be considered as one of diagnostic methods in the context of the DLD when histology is required.

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CCL18 as marker of disease progression in systemic sclerosis

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Background: Lung fibrosis is the most common cause of death in systemic sclerosis. CCL18 is associated with poor prognosis and disease deterioration in fibrotic lung diseases. The prognostic relevance in patients with interstitial lung disease in systemic sclerosis was shown by Tiev et al. (Tiev KP, Eur Respir J 2011 38:1355-1360).
Objectives: To evaluate the role of CCL18 in patients with or without interstitial lung disease in systemic sclerosis.
Methods: We measured the chemokine CCL18 in sera of 126 patients with progressive systemic sclerosis by ELISA, as well as lung function testing at baseline and every 6 months during follow-up. Pulmonary fibrosis was detected by HR-CT. We computed ROC- and Kaplan-Meier-curves and Cox proportional hazards models to analyze the influence of CCL18 on time to disease progression, defined as decline of the predicted FVC -10% or death.
Results: Patients with serum CCL18 concentrations above 140 ng/ml suffered from a significantly higher chance of disease progression ($p<0.0001$) within one year. The hazard ratio to suffer from a disease progression was 8.9 in the univariat Cox hazard model and 8.7 in the multivariate Cox hazard model (after adjusting for age, gender and baseline FVC). In the subgroup of patients without pulmonary fibrosis at baseline the hazard ratio was even 21.1 ($p<0.0001$).
Conclusion: CCL18 predicts disease progression of the lung involvement in patients with systemic sclerosis, independent of age, gender or baseline FVC, especially in patients without any evidence of lung fibrosis. CCL18 in sera might therefore be a tool to identify patients who will suffer from lung function deteroriation in the future and to guide therapeutical interventions in these patients.

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Abnormal heart rate variability in patients with sarcoidosis

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Background: Heart Rate Variability (HRV) can predict cardiovascular events, especially sudden cardiac death and ventricular arrhythmias. Aim of this study was the evaluation of HRV indices in sarcoidosis (Sarc).
Methods: 180 biopsy proven Sarc patients who were not taking antiarrhythmic drugs were included in this study. They were compared with 72 sex and age matched healthy subjects. All participants had pulmonary function tests, cardiac ultrasound, 24-hour Holter monitoring and cardiac MRI and were classified to group A (healthy), group B (cardiac-free Sarc) or group C (cardiac Sarc). The average heart rate (mean HR), the maximum and minimum heart rate (maxHR and minHR), the root mean square of SD of RR (RMSSD) and the standard deviation of all normal to normal NN intervals (SDRR) were calculated during 24-hour Holter monitoring.
Results:

Comparison among groups of different parameters

Parameters	Group A	Group B	Group C	p-Value
FVC	101,5860	95,6689	90,9276	0.01
FEV1	99,9327	92,7135	88,0293	0.001
FEV1/FVC	84,6356	92,4587	89,2151	0.001
TLC	88,2926	84,3371	81,6294	0.008
DLCO	85,27	79,79	71,90	0.0001
KCO	100,040	98,352	91,327	0.003
Mean Heart Rate	76,6806	78,6560	80,0594	0.115
MaxHR	140,2083	136,9322	136,1875	0.4
Min HR	45,0833	48,9365	50,3453	0.013
RMSSD	38,9453	28,7537	29,3037	0.013
SDRR	150,3010	127,2397	112,6206	0.0001

In bivariate analysis, SDRR is correlated with age ($p=0.001$, $r=-.397$), FVC ($p=0.001$, $r=.242$), FEV1 ($p=0.001$, $r=.261$), TLC ($p=0.001$, $r=.290$) and DLCO ($p=0.0001$, $r=.264$).
Conclusion: HRV is decreased in patients with systemic sarcoidosis compared to the control group. SDRR is significantly decreased in patients with cardiac sarcoidosis and is correlated with lung function indices.

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A prosprective study on the safety, tolerability and efficacy of pirfinidone in the treatment of idiopathic pulmonary fibrosis and fibrotic NSIP

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Prospective study conducted on 39 patients with IPF and fibrotic NSIP on patients visiting at Bombay Hospital, Mumbai. Out of 39,9 patients failed to follow up while 9 patients expired on the treatment. Drug had to be stopped in one patient due to reaction. 13% of the patients had a diagnosis proven on surgical lung biopsy. The remaining had their diagnosis confirmed on HRCT, of which 74.4% revelead honey combing and 28% revealed ground-glass opacities.
The mean FVC at baseline has been 1.78lts (57% predicted SD 19%) and 1.57 (61% predicted SD 11.53) at 6 months. The mean corrected DLCO at baseline was 38.29% 39.58% at 6 months. The mean oxygen saturation at baseline 95.38% and 95.82% at 6 months. The 6 min walk test was almost the same at the end of 6 months too (329 vs 331meters). Though patients dropped to a mean saturation of 84.53% post walk at baseline, this did not significantly change 6 months either.
The drug has been quite well tolerated too. None of the patients have elevated liver enzymes and only one patient developed skin rash. GI discomfort and loss of appetite were other side effects that were noted. The average dose of pirfenidone taken during this period was 1082.05 mg/day and the maximum dose administered has been 1800mg/day.
Pirfinidone is the only approved drug for IPF currently available in the world. Considering its previous efficacy documented in slowing the decline in FVC, we thought it appropriate to do this observational study not just on IPF but also on fibrotic diseases to assess its tolerability over a period of time and its potential efficacy in these conditions.

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Strong correlation between 18F-FDG PET positive bone involvement and increased IL-2R levels in patients with untreated sarcoidosis under surveillance (Preliminary results)

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Introduction: F-18 fluorodeoxyglucose positron emission tomography and computed tomography (FDG PET/CT) has been shown to be able to detect osseous involvement in patients with sarcoidosis.
Aim: To use FDG PET/CT to assess bone involvement in therapy-naive sarcoid patients and determine if FDG-avid bone involvement correlates with biochemical markers.
Methods: All patients with a diagnosis of sarcoidosis were identified from a local database in our hospital. Therapy-naive patients under routine surveillance were enrolled in this study, and prospectively underwent a whole-body combined FDG PET/CT scan, as well as biochemical lab tests at the same day, which included interleukin-2 receptor (IL-2R), C-reactive protein (CRP), serum angiotensin-I converting enzyme (SACE), serum calcium and urine calcium levels.
Results: 23 patients (7 male, 49.6 ± 10.4 years) were included. PET(+) bone lesions were identified in 26.1% of the patients (6/23), and all were negative on corresponding CT. SUVmax of the most FDG-avid bone lesion was 9.3 ± 3.4. In patients with PET(+) bone involvement IL-2R was 3000 ± 1588, while in the rest was 982 ± 649. Significant correlation was found between PET(+) bone involvement and increased IL-2R levels only (Spearman's rho=0.621, p=0.002).
Conclusions: The prevalence of FDG PET(+) bone involvement in untreated sarcoidosis is 26.1% in this preliminary series. There is strong correlation between PET(+) bone involvement and increased IL-2R levels and no correlation with abnormal CRP, SACE, serum or urine calcium levels in patients with untreated sarcoidosis.

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Serum from patients with sarcoidosis promotes the proliferation of epithelial cell lines in vitro

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Introduction: Several epidemiological studies have linked sarcoidosis with neoplasia, but this is questioned by many investigators. The present study is an experimental approach to the subject. Our hypothesis was that if sarcoidosis can influence one of the two basic steps of malignancy: cancerous transformation of the cells or out of control cell growth, this could be regarded as an indirect sign of relation to neoplasia.

Materials and methods: A549 and SKMES cell lines were treated with serum from patients with sarcoidosis, COPD and healthy individuals. Their effect on cell proliferation was examined. The influence of cytokines and EGFR on cell proliferation was also investigated.
Results: When serum from patients with sarcoidosis was added to the culture medium of both epithelial cell lines, there was a statistically significant increase of cell proliferation ($p<0.05$). By contrast, serum from normal controls or patients with COPD had no impact. This positive influence of serum from patients with sarcoidosis was annulated by EGFR inhibitor.
Conclusion: Out of control cell growth is a basic step towards malignancy. The increase of epithelial cell proliferation in the presence of sarcoidosis serum, documented in the present study, could represent a link of this disease with neoplasia, under favorable circumstances.

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IL-17a expression in transbronchial biopsy samples in sarcoidosis
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Background: Th17 is a new subset of CD4(+) T cell population and characterized by the release of cytokines such as IL-17A, IL-17F and IL-22. Multiple studies in humans and animals have described the role of Th17 cells in the pathogenesis of several autoimmune and chronic inflammatory diseases such as psoriasis, inflammatory bowel diseases, tuberculosis and lung fibrosis.
Aim: To determine the possible role of Th17 cells in the pathogenesis of sarcoidosis by evaluating the IL-17A levels in lung biopsy samples of sarcoidosis patients.
Method: IL-17A expression was evaluated with immunohistochemical analysis. The area that had higher IL-17A antibody positivity was evaluated with x40 magnification and the positive staining inflammatory cells (macrophage and lymphocyte) were counted.
Results: A total of 41 sarcoidosis patients [32 (78%) female] with the mean age of 48 years were included in the study. Among them 22 (54%) were diagnosed as Stage 1,17 (42%) as Stage 2,1 (%2) as Stage 3 and 4 sarcoidosis.In the whole study group only 2 (5%) patients had no IL-17A(+) inflammatory cells. In the remaining, 9 (22%) patients had one IL17A(+) staining cell, 15 (37%) had 2 cells, 5 (12%) had 3 cells, 9 (22%) had 4 cells and 1 (2%) had 5 cells. The IL-17A (+) staining cells were identified at the periphery of the granuloma. No statistically significant correlation was identified between the number of IL17A(+) staining inflammatory cells and plasma ACE levels, CD4/CD8 ratio and the stage of the disease ($p> 0.05$).
Conclusion: The identification of IL17A (+) staining inflammatory cells in the periphery of the sarcoidosis granulomas, may indicate that Th17 cells have an important role in the pathognesis of sarcoidosis.

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BALF TNFα level in relation to inflammatory status and phenotype of sarcoidosis
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Determining the inflammatory status of the disease may be helpful in predicting the prognosis and responsiveness to treatment.
Aim: To evaluate the relation of BALF TNFα levels to the inflammatory status and phenotype of sarcoidosis.
Material and methods: We have measured: TNFα, TGFβ,IL2, IL2R, IL12, IL10 in BALF and TNFα, TGFβ,IL2, IL12, IL10 levels in serum in 184 sarcoid patients. We checked for the correlations between BALF TNFalpha and cytokines, selected systemic inflammatory markers and clinical factors (age, duration of the disease, PFT, 6MWT, extrapulmonary involvement).
Results: We have found important positive correlation between concentration of BALF TNFα and:
– BALF: IL2R (r=0,4676, p=0,0001), IL12 (r=0,4545, p=0,0001) and serum: IL12 (r=0,26, p=0,001), IL10 (r=0,2832, p=0,001), TNFα (r=0,1871, p=0,12).
– serum CRP (r=0,2427, p=0,003), γglobulins (r=0,1648, p=0,033), Ddimers (r=0,1685, p=0,035).
– the age of patients (r=0,16, p=0,029),
No relation was found between the BALF TNF alpha and the duration of the disease, PFT (except for FEV1 r=-0,1464, p=0,05), 6MWT, extrapulmonary sarcoidosis (liver and spleen dimensions, hepatic enzymes, protrombine), Ca and P serum nor urine levels. Weak but important negative correlation was observed between BALF TNFα and monocytosis (r=-0,1788, p=0,015).
Conclusion: In our group of patients:
The BALF cytokine inflammatory status reflects the systemic inflammation (measured by the serum cytokine network and non-specific inflammatory biomarkers).
The BALF TNFα status has no relation to the phenotype of sarcoidosis.

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Assessing sarcoidosis: The King's Sarcoidosis Questionnaire and the minimal important difference
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Introduction: The King's Sarcoidosis Questionnaire (KSQ) is a brief, validated, multi-organ, health status questionnaire. This study aimed to determine the minimal important difference (MID).
Methods: 60 patients with pulmonary sarcoidosis attending clinic (mean age 52 years,duration 7 years,50% female,67% Caucasian;76% immunosuppressive medications) were asked to complete the KSQ on 2 occasions (change of therapy n=25). Combined Lung-Health Status modules (Lung-HS) consisted of 16 items and impact of medications 3 items; scoring range 0-100,100=best. At the second visit patients also completed a 15-item global rating of change questionnaire (GRCQ). The MID corresponded to the mean change in KSQ in patients indicating a small change in GRCQ ($\pm$ 2/3) and was also estimated by determining 1xSEM and effect size (ES) of 0.3.
Results: Health status was impaired at baseline;mean (SD) Lung-HS 54 (24) and Medication score 60 (29). 20 patients deteriorated,18 improved and 22 were unchanged.The GRCQ scores were associated with change in Lung-HS; r=0.4, $p<0.01$. There was a significant change in Lung-HS score in patients reporting a change in GRCQ; mean (SD) 52 (3) vs 58 (4); 95% CI 1 to 12;p=0.02. The Lung-HS MID determined by GRCQ, SEM and 0.3-ES were 5, 6 and 7 point change respectively. The Lung-HS MID determined by GRCQ for those improving and those deteriorating was 6 and 5 respectively. The MID of individual General HS, Lung and Medication modules determined by GRCQ were 5, 9 and 9 respectively.
Conclusion: The KSQ is responsive to changes in health status and can be used for longitudinal assessment of patients with sarcoidosis. The MID of the combined KSQ Lung-Health Status modules is a 5 point change.